Public Information and Records Integrity Branch
Information Resources and Services Division, 7502C
Office of Pesticides Programs
Environmental Protection Agency
Room 119
Crystal Mall #2
1921 Jefferson Davis Highway
Arlington, VA

Attention: Docket ID Number OPP-2002-0350

April 7, 2003

Comments to EPA re: Dow Agro Request for a Tolerance for Corn Rootworm Transgenic Corn Containing Cry34Ab1/Cry35Ab1

Center for Science in the Public Interest (CSPI) submits the following comments recommending that EPA deny DowAgro Science's request for a food tolerance or an exemption from tolerance for its new rootworm-protected corn containing Cry34Ab1/Cry35Ab1 (hereafter Cry34/35). This exemption would allow DowAgro to incorporate Cry34/35 corn into the food supply when grown under an experimental use permit (EUP). We make our recommendation based on simulated gastric digestion (SGD) data submitted to EPA by DowAgro indicating that Cry34Ab1 may become a food allergen if allowed into the food supply. Furthermore, due to the limitations of current allergencity tests, we highly recommend that EPA present the allergencity data for Cry34/35 to independent experts on allergenicity, such as the Scientific Advisory Panel, before making a decision on the full registration of Cry34/35 in the future.

We find that SGD data for Cry34/35 presented in MRID 455845-02 and MRID 452422-12 indicate that Cry34Ab1 should be considered to be stable according to accepted scientific literature, and therefore disagree with Dow Agro's interpretation of instability of Cry34Ab1. While digestive stability does not prove that a protein will become a food allergen it has been accepted by international groups of experts on allergencity as indicating a reasonable likelihood of allergenicity (Astwood et al., Metcalfe et al., United Nations Food and Agriculture Organization/World Health Organization). Therefore, EPA cannot determine with reasonable certainty that Cry34Ab1 will not cause allergic reactions when consumed.

DowAgro presents two sets of data concerning SGD which found that intact Cry34Ab1 could be detected for 20-30 minutes using sensitive detection methods (Western blot), or that 90% of Cry34Ab1 was digested after 6.2 minutes using less sensitive detection methods (Coomassie-stained SDS-PAGE gel). DowAgro discounts the 20-30 minute stability data by claiming that the detection method (Western blot) was more sensitive than in SGD for previous Cry proteins registered by EPA. Based on their

calculation of 90% digestion of Cry34Ab1 after 6.2 minutes, DowAgro concludes that Cry34Ab1 is not stable.

DowAgro's interpretation of SGD data is not in accord with currently accepted standards for several reasons. First, literature such as that cited by DowAgro on SGD finds that several food allergens were digested in as few as two to eight minutes (Astwood et al., Metcalfe et al.). By that criterion, detection of Cry34Ab1 after 6.2 minutes would indicate stability, not instability (see Astwood et al., Table 1).

Furthermore, the cited literature uses the longest time-point where SGD test protein can be detected as a measure of stability, not the rate of digestion used by DowAgro to determine 90% digestion. For example, Astwood et al. use the longest time-point for which food allergens can be observed as their measure of stability. Like DowAgro, they use Coomassie-stained SDS-PAGE gels to detect undigested allergens. Cry34Ab1 is visible, even under the poorly reproduced gel pictures found in MRID 455845-02 and MRID 452422-12, for up to 20 minutes, and clearly visible at 7.5 to10 minutes in most of the gels.[1]

In addition, DowAgro uses more than three-fold higher proportion of pepsin-to-test-protein (Cry34Ab1) in its SGD assay compared to Astwood et al., which may make Cry34Ab1 appear to be less stable than it would if carried out according to the literature. Recent experiments clearly demonstrate that the proportion of pepsin to allergen can change the apparent stability of the allergen (T.J. Fu and Fu et al.). More recent protocols recommend even lower pepsin to test protein proportions (United Nations Food and Agriculture Organization/World Health Organization). These more recent protocols also recommend detecting SGD test protein using silver staining or colloidal gold which is more sensitive than Coomassie staining and may approach the sensitivity of the Western blots used by DowAgro that showed 20-30 minute stability of Cry34Ab1.

We recognize that the limited dietary exposure, both in amount and duration, that would be caused by granting a temporary tolerance for Cry34/35 makes the likelihood of allergic reaction low. However, it is a chance that should not be taken. DowAgro could continue to grow Cry34/35 corn under an EUP on a crop-destruct basis if other safety criteria are found to be acceptable. Therefore, it would be especially imprudent to approve the requested tolerance.

Finally, the dilemma presented by the current lack of tests that would more clearly determine the potential allergencity of a protein new to the food supply is obvious in the example of Cry34/35. This example emphasizes the crucial need for the development of more definitive tests and, in their absence, the delineation of acceptable standards for performing and interpreting currently available tests such as SGD. Such standards are provided by the FAO/WHO expert consultation on food allergy assessment for GE proteins (United Nations Food and Agriculture Organization/World Health

[1] The regression analysis provided by DowAgro to determine the 90% digestion time was not accompanied by any statistical analysis of variance, such as a confidence interval. Therefore, given the apparent variability observed on the detection gels, it is possible that the 6.2 min. DT_{90} is not statistically significant.

Organization), and EPA should adopt those standards. Until such measures are taken, EPA will continue to face situations that may challenge the credibility of its decisions, and hence public confidence in GE technology.

Sincerely,

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